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(54) Title: FLUIDIC COUPLERS AND MODULAR MICROFLUIDIC SYSTEMS

(57) Abstract: A modular microfluidic system including a plurality of discrete microfluidic modules and at least one microfluidic coupling device for communicating fluid between the modules is described. The microfluidic modules and coupling devices may be constructed according to various techniques. Each coupling device is fabricated from multiple layers and includes a fluidic inlet port, a fluidic outlet port, and at least one sandwiched stencil layer having a microfluidic channel formed therein. Also described are integrated microfluidic systems capable of performing various functions.

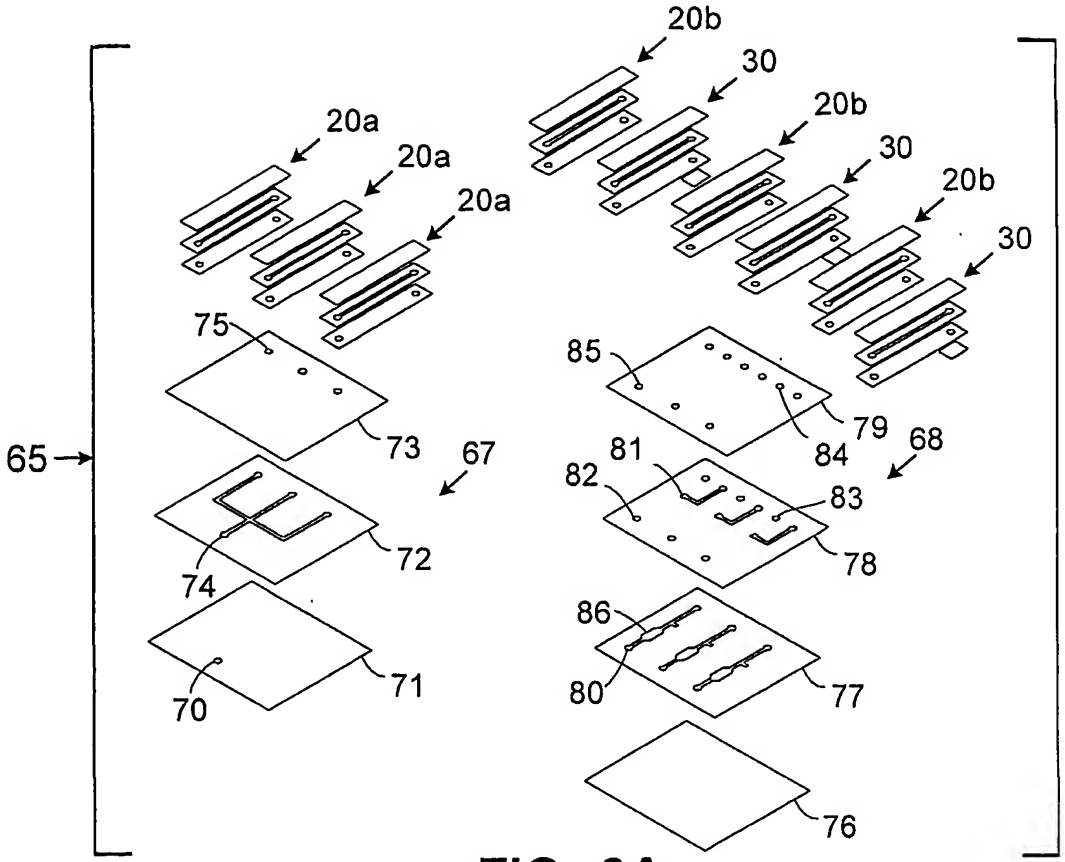
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FIG._3A

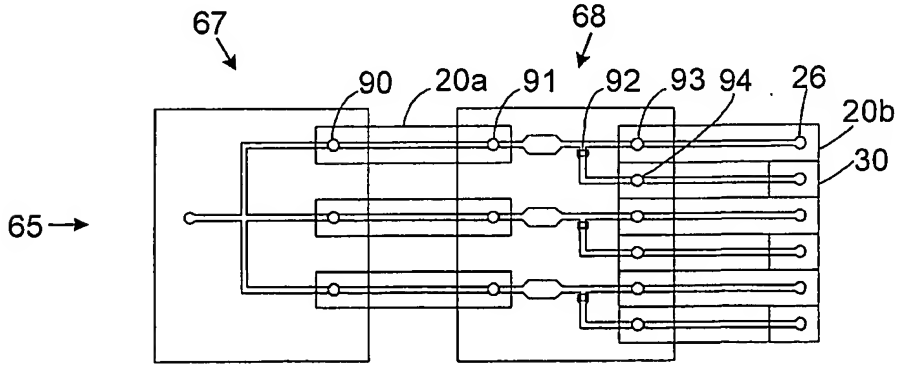
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FIG._3B

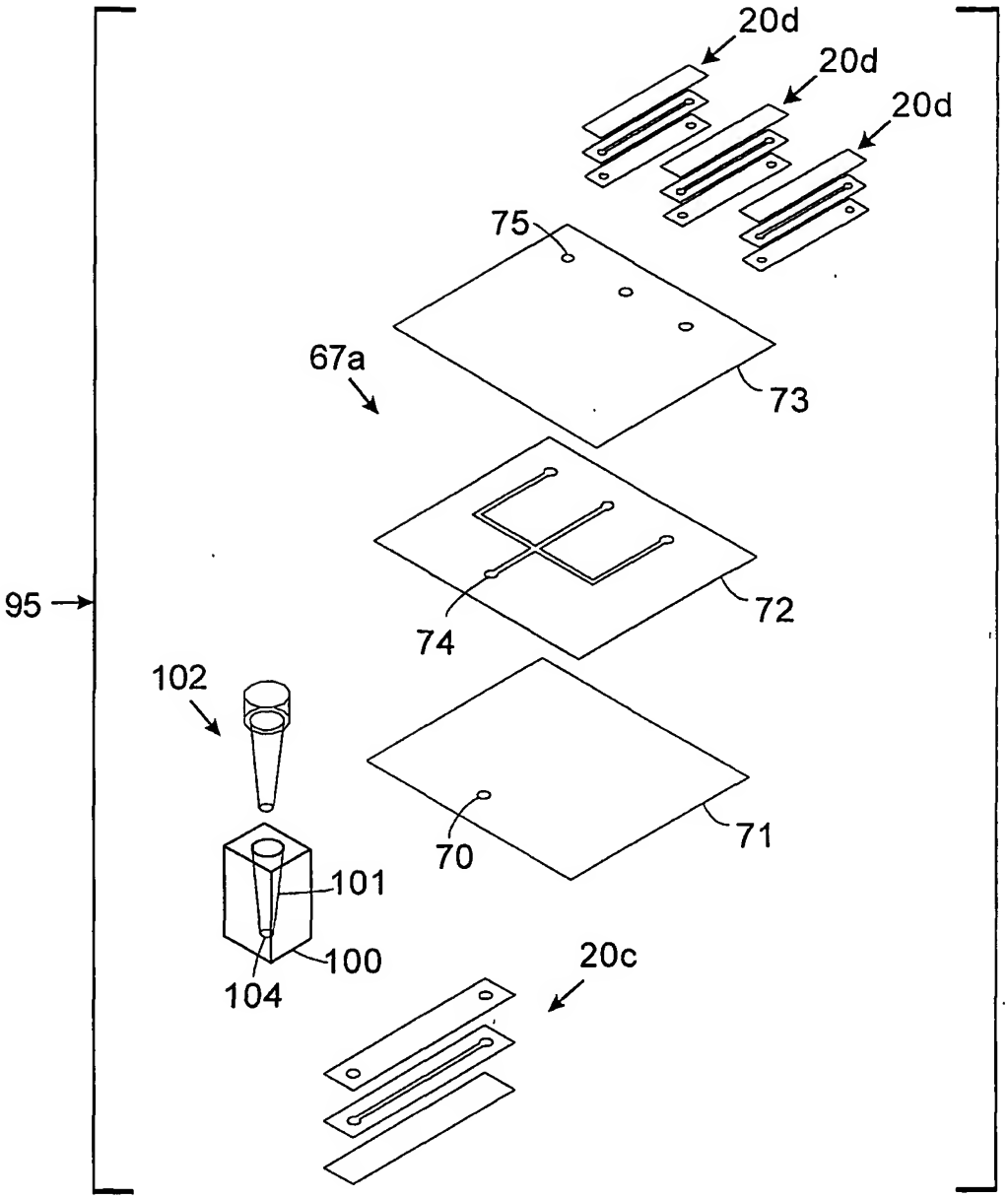

FIG._4A

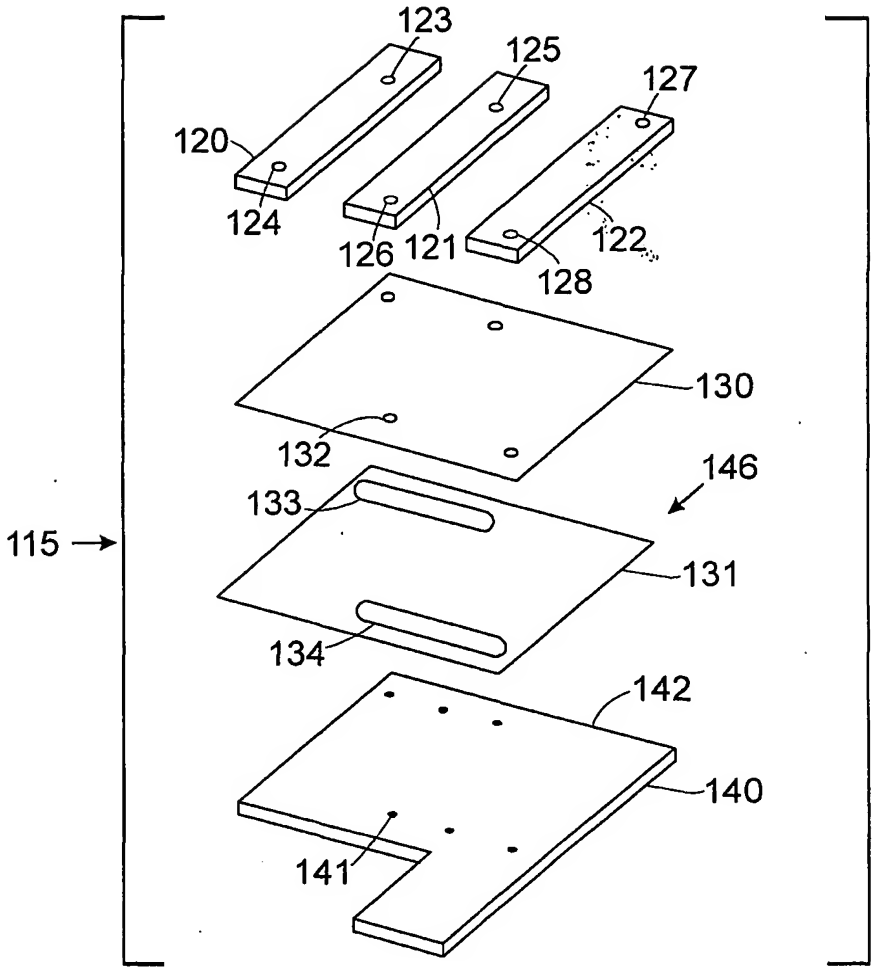

FIG._5A

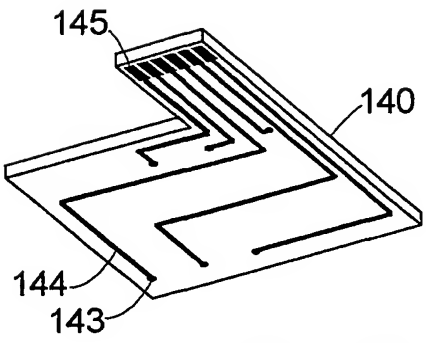

FIG._5B

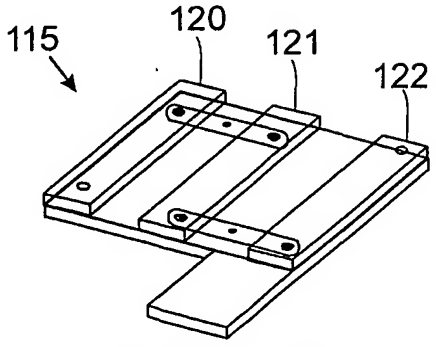

FIG._5C

TITLE OF THE INVENTION

FLUIDIC COUPLERS AND MODULAR MICROFLUIDIC SYSTEMS

FIELD OF THE INVENTION

[0001] The present invention relates to microfluidic devices, and, more particularly, to the introduction of fluid into and removal of fluid from microfluidic devices, and the integration of modular microfluidic systems.

BACKGROUND OF THE INVENTION

[0002] There has been a growing interest in the manufacture and use of microfluidic systems for chemical and biochemical manufacturing processes and the acquisition of chemical and biological information. In particular, microfluidic systems allow complicated biochemical reactions to be carried out using very small volumes of liquid. These miniaturized systems increase the response time of the reactions, minimize sample volume, and lower reagent cost.

[0003] Traditionally, microfluidic devices and components have been constructed in a planar fashion using photolithography to define channels on a silicon or glass substrate followed by etching techniques to remove material from the substrate to form channels. More recently, a number of methods have been developed that allow microfluidic devices to be constructed from plastic, silicone or other polymeric materials. In addition to the use of traditional injection cavity molding, the wide variety of molding steps or methods (generally involving the construction of a negative mold and then inserting material into or over the mold) that have been developed for constructing microfluidic devices include: fabricating molds with silicon wafers (*e.g.*, Duffy, *et al.*, Analytical Chemistry (1998) 70: 4974-4984 and McCormick, *et al.*, Analytical Chemistry (1997) 69: 2626-2630); building components using a LIGA technique (*e.g.*, Schomburg, *et al.*, Journal of Micromechanical Microengineering (1994) 4: 186-191) as commercialized by MicroParts (Dortmund, Germany); and combining LIGA fabrication steps with hot-embossing techniques, as performed by Jenoptik (Jena, Germany). Imprinting methods for producing microfluidic devices in PMMA have also been demonstrated (*e.g.*, Martynova, *et al.*, Analytical Chemistry (1997) 69: 4783-4789). Still further methods for constructing other types of microfluidic devices have been provided, by the same applicant herein, in two published WIPO PCT patent applications, nos. PCT/US00/27313 (WO 01/25137) and PCT/US00/27366 (WO 01/25138). Such methods

include construction of microfluidic devices using circuit board and sandwiched stencil fabrication methods.

[0004] Thus, there exist several different types of microfluidic devices, manufactured according to several different techniques. Despite the desirability of interconnecting or integrating such devices, however, to date no simple interconnection or integration methods or devices have been available. For example, a preparation system may be constructed using silicon fabrication technology while a sorting device might be constructed using a silicone replication technique (*see*, Fu, *et al.*, Nature Biotechnology (199) 17: 1109-1111). Though it would be desirable to combine such preparation and fabrication devices in a single integrated device, it would be difficult, if not impossible, to accomplish.

[0005] Moreover, discrete microfluidic components that perform specialized functions are often constructed. It would be desirable to quickly integrate such components into a complete system. For example, a silicon-based microfluidic sample preparation component can be constructed. A separate microfluidic detection component could also be constructed. To make a completed device, the developer must typically go back to the development stage and develop processing techniques and steps that allow a single integrated device to be developed.

[0006] Another issue in the development of microfluidic systems is the manner in which fluids and samples are introduced into and removed from a microfluidic device or system. It would be desirable to provide interface means that would permit fluids to be quickly and simply introduced or removed from such devices, and particularly for such an interface to be compatible with various types of microfluidic devices.

[0007] Therefore, a great need exists for a device or method for connecting together different types of microfluidic devices, such as may have been manufactured using different techniques. A further need exists for integrating discrete microfluidic components into a complete system. A still further need exists for aiding in the introduction and removal of fluids to and from microfluidic devices or systems.

SUMMARY OF THE INVENTION

[0008] Using at least one coupling device, multiple microfluidic modules or devices may be connected together to form a larger system. If desired, complex microfluidic systems may be constructed by coupling discrete modules or devices.

[0009] In one aspect of the invention, a modular microfluidic system includes a plurality of discrete microfluidic modules and at least one microfluidic coupling device for communicating fluid between the modules. Each module is adapted for rapid attachment or

detachment from one or more other modules and is capable of performing a desired function independently from any other module. Each coupling device (if more than one is present) is fabricated from multiple layers and includes a fluidic inlet port, a fluidic outlet port, and at least one sandwiched stencil layer having a microfluidic channel formed therein.

[0010] In a separate aspect of the invention, a microfluidic coupling device used to connect a plurality of discrete microfluidic modules may be constructed to be flexible.

[0011] In another separate aspect of the invention, at least one microfluidic coupling device may include a plurality of discrete, integral electrodes.

[0012] In another separate aspect of the invention, a removable connection between the multiple microfluidic modules may be provided.

[0013] In yet another aspect of the invention, any of the foregoing separate aspects may be combined for additional advantage.

[0014] These and other aspects and advantages of the invention will become apparent to the skilled artisan upon review of the appending description, drawings, and claims.

Definitions

[0015] The term "channel" or "chamber" as used herein is to be interpreted in a broad sense. Thus, it is not intended to be restricted to elongated configurations where the transverse or longitudinal dimension greatly exceeds the diameter or cross-sectional dimension. Rather, such terms are meant to include cavities or tunnels of any desired shape or configuration through which liquids may be directed. Such a fluid cavity may, for example, comprise a flow-through cell where fluid is to be continually passed or, alternatively, a chamber for holding a specified, discrete amount of fluid for a specified amount of time. "Channels" and "chambers" may be filled or may contain internal structures comprising valves or similar fluidic components.

[0016] The term "microfluidic" as used herein is to be understood, without any restriction thereto, to refer to structures or devices through which fluid(s) are capable of being passed or directed, wherein one or more of the dimensions is less than 500 microns.

[0017] The term "module" as used herein refers to a discrete microfluidic component or microfluidic device that may be utilized within a microfluidic system. Preferably, microfluidic modules may be interconnected in various ways using microfluidic coupling devices.

[0018] "Substantially planar" as used herein refers to a structure having a height of between about 1 and 500 microns and a length and width each at least 100 times larger than the height.

[0019] A "stencil layer" as used herein refers to a discrete layer of material through which a channel or aperture has been cut through the entire thickness of the layer. The outlines of the cut or otherwise removed portions form the lateral boundaries of microstructures, preferably microfluidic channels, that are formed by sandwiching one or more stencil layers between other stencils and/or substrates. The stencils and substrates are preferably substantially planar. Stencil layers are bonded by any technique that results in substantially liquid-tight channels within the device.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1A** is an exploded perspective view of a three-layer microfluidic coupling device. **FIG. 1B** is a top view of the assembled device of **FIG. 1A**. **FIG. 1C** is an exploded perspective view of a four-layer microfluidic coupling device. **FIG. 1D** is a top view of the assembled device of **FIG. 1C**.

[0021] **FIG. 2A** is an exploded perspective view of a microfluidic metering and coupling system including a four-layer microfluidic metering device or module and three microfluidic coupling devices. **FIG. 2B** is a top view of the assembled microfluidic metering and coupling system of **FIG. 2A.**

[0022] **FIG. 3A** is an exploded perspective view of a microfluidic system including a three layer microfluidic distribution device or module, a four-layer microfluidic filtering device or module, three microfluidic coupling devices for coupling the distribution and filtering devices, and six microfluidic coupling devices to be connected to outputs of the filtering device. **FIG. 3B** is a top view of the assembled microfluidic system of **FIG. 3A.**

[0023] **FIG. 4A** is an exploded perspective view of a microfluidic coupling and distribution system including a fluidic introduction device or module, an input microfluidic coupling device, a microfluidic distribution device or module, and three output microfluidic coupling devices. **FIG. 4B** is a perspective view of the assembled system of **FIG. 4A.**

[0024] **FIG. 5A** is an exploded top perspective view of a microfluidic multichip module system having integral electrodes disposed in the lowermost chip or layer. **FIG. 5B** is a bottom perspective view of the lowermost chip or layer showing wire traces for the integral electrodes. **FIG. 5C** is a top perspective view of the assembled system of **FIG. 5A.**

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

[0025] According to the present invention, modular microfluidic systems include microfluidic coupling devices that are used to communicate fluid between multiple microfluidic modules. The coupling devices may be used for the introduction of fluid into

and removal of fluid from microfluidic modules, or for the integration of modular microfluidic systems.

[0026] Microfluidic modules or devices according to the present invention may be fabricated in various ways using a wide variety of materials. In a preferred embodiment, microfluidic modules according to the present invention are constructed using stencil layers to define structures such as channels and/or chambers by removing material through the entire thickness of the layer. To facilitate convenient material removal, a computer-controlled plotter modified to accept a cutting blade may be used. Alternatively, a computer-controlled laser cutter may be used. As further alternatives, conventional stamping, cutting, and/or molding technologies may be employed. The wide variety of materials that may be used to fabricate microfluidic devices using sandwiched stencil layers include polymeric, metallic, paper, and/or composite materials, to name a few. When assembled in a microfluidic device, the top and bottom surfaces of stencil layers may mate with one or more adjacent stencil or substrate layers to form a substantially enclosed device.

[0027] Referring to **FIGS. 1A-1B**, a microfluidic coupling device 20 having a substantially planar first substrate layer 21 and a substantially planar second substrate layer 23 is provided. The second substrate layer 23 has a lower surface that defines the bottom of the microfluidic coupling device 20. The coupling device 20 also has at least one substantially planar stencil layer 22 disposed between, or "sandwiched" between, the first and second substrate layers 21, 23. The stencil layer 22 has at least one channel 24 formed in it, with at least one dimension less than about 500 microns. The channel 24 is in fluid communication with a first aperture or fluid port 25 defined in the second substrate layer 23. The channel 24 is preferably vented to allow fluid to flow. Although not required in all embodiments, the coupling device 20 contains a second aperture or fluid port 26 in the second substrate layer 23. The second fluid port 26 is in fluid communication with the channel 24. In some embodiments, the second fluid port 26 may be defined in the first substrate layer 21. Alternatively, all or a portion of either substrate layer 21, 23 can be a semi-permeable membrane that allows the passage of gas, but substantially prevents the passage of liquids.

[0028] For devices of the type shown in **FIGS. 1A-1B**, adjacent surfaces of the various layers are complementary so as to seal against a sandwiched stencil layer. Notably, one or more stencil layers may be provided in a single coupling device. For example, combinations of mating layers may include substrate-stencil-substrate, substrate-stencil-stencil-substrate, or many others. Stencil and substrate layers may be stacked or layered to provide a complex microfluidic device. Most preferably, the mating layers are

substantially planar. Stencils and substrate layers may be constructed from any suitable materials, including preferably MYLAR®, polyester, polyimide (*e.g.*, KAPTON®) and adhesive tapes. One or more materials are preferably used to coat, seal, and/or adhere the channels formed between the substrates. Where the layers are constructed from adhesive tapes, the tapes can be pressure-curing tapes, temperature-curing tapes, chemical-curing tapes, light-curing tapes, or other types of curing tapes.

[0029] In one embodiment, one or more stencil layers are fabricated from single- or double-sided adhesive tape. A portion of the tape (of the desired shape and dimensions) can be cut through the thickness of the tape and removed to form, for example, a channel or entry/exit ports. The tape stencil can then be arranged between one or more supporting substrates or other stencil layers. In one embodiment, similarly-configured stencil layers can be stacked on one another. In this embodiment, the thickness or height of the resulting channels can be varied by simply varying the thickness of the stencil. If a tape stencil is used, then the total thickness includes the thicknesses of both the tape carrier and the adhesive or glue thereon.

[0030] In certain embodiments, double-sided tape may be used in constructing the coupling devices, and various substrate materials may be used for the other stencil layers. For example, in one embodiment configured as the coupling device 20 in **FIGS. 1A-1B**, stencil layer 21 is constructed from a MYLAR® material, stencil layer 22 from double sided tape and stencil layer 23 from single sided tape with a MYLAR® backing. In this manner, the upper and lower boundaries of the channel 24 are both MYLAR® material.

[0031] In a preferred embodiment, adhesive is used to connect a microfluidic coupling device to a separate microfluidic module or device. In a more preferred embodiment, the adhesive surface used to couple the microfluidic coupler to the microfluidic device is a non-permanent adhesive, such as are many types of pressure-sensitive adhesives. In this manner, a coupling device can be physically and fluidically connected to a microfluidic device, fluid may be communicated through the coupling device, and thereafter the microfluidic coupler may be removed. In another preferred embodiment, the surface used to couple the microfluidic coupling device to an external microfluidic device or module is made tacky with a substance such as silicone.

[0032] In one embodiment, the microfluidic coupling device is flexible. The entire coupling device can be constructed of various films, papers, tapes, plastics and the like such that the resulting coupling device is flexible. Flexibility can aid in aligning a microfluidic coupling device to another microfluidic device or can facilitate coupling two distinct microfluidic devices or modules. Materials used for fabricating a microfluidic coupling device may also be malleable. Such malleability aids in sealing a microfluidic coupling

device with another device, especially in cases where the mating surface of the target device is uneven.

[0033] The microfluidic coupling device 20 of **FIG. 1A** can be constructed such that the lower surface of the second substrate 23 has an adhesive coating and such that one or more of the ports 25, 26 connects through the second substrate 23. Preferably, this adhesive coating is integral to the layer, such as provided by a self-adhesive tape. The device 20 also can be constructed such that the upper surface of the first substrate layer 21 has an adhesive, preferably self-adhesive, coating. In an alternative embodiment, a coupling device may be provided with two ports, the first port defined in the first substrate layer and the second port in the second substrate layer, with both the upper surface and lower surface having adhesive coatings. Such an embodiment allows the coupling device to be rapidly connected to external microfluidic devices or modules. The adhesive used may be either a permanent adhesive or a removable adhesive. In such an alternative embodiment, the device may also include a backing layer removably adhered to the adhesive lower surface of the second substrate. The backing material protects the adhesive material from inadvertent contact or adhesion with undesired objects until such a time as the microfluidic coupling device is to be attached to another microfluidic device. The backing material may be any suitable plastic, paper or foil.

[0034] In a further embodiment, a semi-permeable membrane permitting the passage of gases but substantially blocking the passage of liquids may be added to a microfluidic coupling device. Referring to **FIGS. 1C-1D**, for example, a microfluidic coupling device 30 is configured identically to the device 20 illustrated in **FIGS. 1A-1B** except for the addition of a semi-permeable membrane 27 covering the second fluidic port 26. The semi-permeable membrane 27 allows gases to pass, but substantially disallows the passage of liquid. For example, a suitable semi-permeable membrane will allow air to pass through it, but will not allow water to pass. The desired effect may be achieved by selecting a semi-permeable membrane with a suitable pore size. In one embodiment, the semi-permeable membrane 27 is a polymeric material with a pore size of less than about 75 microns, and preferably less than about 10 microns. Examples of such filter materials include Porex Technologies (Fairburn, GA) X-7744 (7 micron pore size) and GORETEX®-type materials.

[0035] With multiple ports provided in a single microfluidic coupling device, a first fluidic port may be used to admit liquid and a second fluidic port may be used as a vent for air escape. Alternatively, the second fluidic port may be used as a liquid exit port rather than a vent. A fluidic inlet port may be directly coupled to another microfluidic device or module using an adhesive. The adhesive may be disposed on a surface of the coupling device, on a surface of the target microfluidic device or module, or both.

[0036] In another preferred embodiment, porous materials can be used at the outlet of a microfluidic coupling device to add impedance to a fluidic system. These materials can be chosen so that they have slight resistances to the passage of air or gas, but provide very large resistance to the passage of liquid. The pore size and material composition can be selected to produce the desired effects and impedances. For a functional microfluidic device or module having multiple fluidic exit ports, multiple microfluidic coupling device may be used, with one coupling device associated with each exit port. One or more different coupling devices each having an outlet port may have porous materials associated with these outlet ports. Different porous materials may be associated the outlet ports of different coupling devices. In this manner, the coupling device outlet materials can be used to produce preferential fluid flow within a multi-outlet microfluidic device to which multiple coupling devices are connected.

[0037] Referring to **FIGS. 1A** and **1C**, in a preferred embodiment the bottom surface of 28 of a microfluidic coupling device 20 or 30 is provided with an adhesive material adjacent to the first fluidic port 25 to allows the port 25 to be connected to the a fluidic exit port of a separate microfluidic device or module (not shown). Alternatively, the surface 28 can be non-adhesive yet still mate with an adhesive surface on the separate microfluidic device or module to which coupling is desired. In an alternative embodiment, mating surfaces of both a coupling device and a target microfluidic device or module are provided with adhesives.

[0038] An adhesive can be placed on the outer surface 28 of a microfluidic coupling device 20 or 30 in various ways. In a preferred embodiment, the bottom surface 28 of layer 23 is inherently adhesive, such as when the layer 23 is composed of self-adhesive tape with a downward-facing adhesive surface. In other embodiments, a coating may be placed on the bottom surface 28 of layer 23 either before or after assembly of the microfluidic coupling device. This coating can be accomplished in a number of ways, including spin coating, spray coating, and vacuum deposition.

[0039] In certain embodiments, it may not be desirable to have a fluidic port of a microfluidic coupling device open to the environment. Also, in some embodiments, a microfluidic coupling device may have a flap of material for sealing either the first or second fluidic port In a preferred embodiment, a port is disposed in an adhesive lower surface of a coupling device, and the flap is an extension of the second substrate.

[0040] Channels within microfluidic coupling devices according to the present invention may also be derivatized with a chemical or biological moiety in order to perform a binding or separation function. Referring again to **FIG. 1A**, a microfluidic coupler 20 may be constructed starting with an upper layer 21 constructed from a thin sheet of glass that is

approximately ¼" (6 mm) wide by 1 ½" (49 mm) long by 1/32" (0.75 mm) thick. The stencil layer 22 may be constructed from 3.4 mil (83 microns) thick double-sided tape with a 40 mil (100 microns) wide channel. Finally, layer 23 may be constructed from a single-sided piece of adhesive tape with 0.08" (2 mm) diameter inlet/outlet ports 25, 26. Prior to assembly, the glass layer 21 may derivatized using a typical silanization reaction. Genetic probes can then be bound to the surface of the glass.

[0041] In operation, a fluidic sample is manipulated within a microfluidic module (not shown) and passed into the microfluidic coupling device 20. The sample may contain labeled genetic stands of interest that can bind to the surface of the derivatized glass 21. After incubation, the channel 24 of the microfluidic coupling device 20 may be washed to remove non-specifically bound material. The glass surfaces of the channel 24 can then be analyzed to determine if the labeled genetic material of interest is present. For instance, the genetic samples may be fluorescently labeled and the fluorescence of the channel studied. Notably, other types of surface chemistry may also be utilized, such as anti-body binding to polystyrene or Teflon or other materials.

[0042] In another aspect of the invention, a modular microfluidic system made from a plurality of microfluidic modules is provided. Preferably, each microfluidic module is adapted for rapid attachment to or detachment from one or more other modules, and is self-contained for performing a desired function independently of each other module. In a preferred embodiment, the microfluidic modules are attached to each other using the microfluidic coupling devices shown in **FIGS. 1A-1D**. As would be obvious to a skilled artisan, microfluidic modules may have one or more fluid inlet ports and one or more fluid outlet ports. In a preferred embodiment, these modular microfluidic systems can be made from modules that perform chemical or biochemical synthesis or chemical or biochemical analysis. The modular microfluidic systems may also be designed for use in either continuous processing mode or in batch processing mode.

[0043] As discussed in the background section above, microfluidic modules for use with the modular microfluidic systems may be constructed using various techniques, including photolithography / etching, micromolding, various LIGA methods (whether or not coupled with hot embossing), imprinting in PMMA, and by using circuit board and/or sandwiched stencil fabrication methods. The microfluidic modules are also capable of being used with a variety of pumping and valving mechanisms, including pressure, peristaltic pumping, electrokinetic flow, electrophoresis, vacuum and the like. Miniature pumps and valves may be constructed to be integral within such modules, although separate or off-line pumping or valving mechanisms are contemplated. In addition, the microfluidic modules are capable of being used in conjunction with optical detection (e.g.,

fluorescence, phosphorescence, luminescence, absorbance and colorimetry), electrochemical detection, and any of various suitable detection methods. Suitable detection methods will depend on the geometry and composition of the device. The choice of such detection methods will be within the purview of the skilled artisan.

[0044] Within existing technology, a microfluidic device typically performs a function on a sample and once that function is completed, it becomes necessary to transport the fluid off the device for further analysis. In a preferred embodiment of the present invention, a microfluidic multi-chip module (MCM) is constructed to facilitate transport of samples between more than one microfluidic module.

[0045] In one embodiment, one or more microfluidic coupling devices may be used to capture fluid that has been manipulated in a microfluidic device to promote further analysis or manipulation in a multi-step laboratory experiment. For example, **FIGS. 2A-2B** illustrate a microfluidic metering and coupling system 35 including a metering device 36 and three associated microfluidic coupling devices 30. The microfluidic metering device 36 is capable of receiving a quantity of sample having a large volumetric standard deviation, metering off a discrete amount having a much smaller volumetric standard deviation, dividing the metered amount into three equal components, and finally transporting the sample off-board for further analysis using the microfluidic coupling devices 30.

[0046] Referring to **FIG. 2A**, a metering device 36 useful with a modular microfluidic system is composed of six layers 41-46. The first layer is a 1/8" (3.2 mm) thick polycarbonate base 41 defining a fluidic inlet port 40. Five stencil layers 42-46 have channels 47-54 cut into them, with three fluidic outlet ports 55 defined in the third layer 44. Stencil layers 42-44 may be constructed from single-sided adhesive tape such as, for example, a 3 mil (76 micron) thick polypropylene carrier with permanent water-based adhesive. Smaller stencil layer 45 may be constructed from double-sided tape, such as, for example, 0.5 mil (13 microns) thick polyester carrier with acrylic adhesive on both sides. Further, stencil layer 46 may be constructed from a porous material such as 30-60 micron (pore size PTFE (Norton A-125). The stencil layers 42-46 are adhered together and onto the base layer 41.

[0047] The three microfluidic coupling devices 30 are constructed using stencil layers. A first layer 21 covers a channel 24 defined in a second layer 22 a 21-23, at least one of which may be composed of single-sided tape such as a 3 mil (75 micron) thick polypropylene carrier with water-based adhesive. The coupling devices 30 are 0.25" (6 mm) by 1-3/8" (34 mm) in dimension. A channel 24 that is 0.04" (1 mm) wide and 1-1/8" (28 mm) long is cut into the second stencil layer 22, and inlet and outlet ports 26 (0.08" or 2 mm diameter) are cut into the third stencil layer 23. A porous membrane 27 such as Norton

G115 (1-2 micron pore size PTFE), cut into a ¼" by ¼" (6 mm by 6 mm) section, is adhered to the bottom surface of the third layer 23. All four layers 21, 22, 23, 27 are adhered together to form the assembled microfluidic coupling device 30.

[0048] The assembled modular microfluidic metering and coupling system 35 is shown in **FIG. 2B**. As assembled, the system 35 includes four different types of overlap regions 60-64 (overlaps 62 and 63 are identical) at the interfaces between fluidic structures disposed in different layers. Notably, each overlap region 60-64 provides an opportunity to form an impedance for controlling the movement of fluid within the device 36. If the overlap is very small in flow area, the impedance will be large, while if the overlap has a large flow area then the impedance will be smaller. These overlap-type impedance regions are particular useful in controlling developing flow, that is, flow that is progressing within the device along a liquid-gas (such as water-air) interface. All of the channels 47-54 are 3 mils (75 microns) high, thus the overlap regions are 6 mils (150 mils) high. At overlap 60, both channels are 40 mils (1000 microns) wide and they overlap for 40 mils (1000 microns). At overlap 61, channel 48 is 40 mils (1000 microns) wide and tapers down to 20 mils (500 microns) in the overlap region; channel 50 is 40 mils (1000 microns) wide and channel 48 extends across channel 50 for 20 mils (500 microns). At identical overlaps 62 and 63, the entry channels 48, 49 are 40 mils (1000 microns) wide, the exit portions are 70 mils wide (1000 microns) and the overlap is 40 mils (1000 microns) in length. The inlet ports 25 of the microfluidic coupling devices 30 are placed on top of the outlet ports of the microfluidic device 55 and the adhesive tape on the bottom surface of the microfluidic coupling devices 30 is used to seal the junction 64.

[0049] In operation, a sample plug is injected onto the microfluidic metering device 36 at the inlet port 40 using a syringe pump at a constant flow rate. A fluidic impedance 60 is constructed immediately after the inlet port 40 to control the initial fluid flow. The fluid then passes into channel 50 and fills the channel 50 until it reaches impedance 62. At this point, the excess fluid within the sample breaks through the microfluidic impedance at the overlap 61 before the microfluidic impedance at the overlap 62. The excess fluid passes down channel 48. Once all of the excess fluid has passed through the waste channels (48, 51 and 54) it reaches the porous material 46. The excess fluid will not pass the porous material 46 and the microfluidic impedance 62 is overcome. The amount of sample now ready for further manipulation is defined by the volume of channel 50 between the two microfluidic impedances 61 and 62. If a different sample volume is desired, then the position of the microfluidic impedance region 61 can be moved along channel 50 to alter the volume.

[0050] Once the air in channel 48 has been compressed sufficiently to build up enough pressure, microfluidic impedance 62 is overcome. The sample now enters chamber 49 and fills the entire chamber up to the impedances 63. Once this chamber has been completely filled, the output microfluidic impedances 63 are overcome and the samples enter into the inlet ports 55 of the microfluidic coupling devices 30 and enter into the channels 24 of the coupling devices 30. Once all of the coupling devices 30 are filled, the coupling devices 30 may be removed to permit the samples within the coupling device 30 to be analyzed with an "off board" technique, such as scintillation counting (*e.g.*, for biomolecules labeled with 32P) or fluorescence analysis.

[0051] In another embodiment, a microfluidic system may utilize multiple sets of microfluidic coupling devices to interconnect multiple microfluidic devices. For example, referring to **FIG. 3A**, a microfluidic system 65 includes a first set of coupling devices 20a to deliver fluid from a microfluidic distribution device 67 to a microfluidic filtering device 68, a second set of coupling devices 30 to control fluid flow, and a third set of coupling devices 20b to transport the fluid off the filtering device 68 for further analysis. The distribution device 67 may be constructed from a 1/8" thick polycarbonate base 71 defining an inlet port 70 and two stencil layers 72, 73. The stencil layer 72, 73, which define a channel 74 and exit ports 75, are constructed from single-sided adhesive tape consisting of 3 mil (75 micron) polypropylene carrier with a permanent water-based adhesive. The channel 74 is 500 microns wide and the outlet ports 75 are 0.08" (2 mm) diameter. The stencil layers 72, 73 are adhered together and onto the base 71.

[0052] A filtering device 68 may be similarly constructed by adhering three stencil layers 77-79 onto a 1/8" (3.2 mm) thick polycarbonate base 76. The stencil layers 77-79 define channels 80, 81, through-holes 82, 83, inlet ports 85 and outlet ports 84. All of the through-holes and ports are 0.08" (2 mm) in diameter.

[0053] The microfluidic couplers 30 are identical to those shown in **FIGS. 2A-2B**. The microfluidic couplers 20a, 20b are identical to the microfluidic couplers 30 with the exception that no porous material was added.

[0054] The assembled system 65 is shown in **FIG. 3B** and contains five different types of overlap regions 90-94. At overlap region 90, fluid passes from the distribution device 67 into microfluidic couplers 20a. At overlap region 91, fluid passes from the microfluidic couplers 20a into the filtering device 68. Two channels 80 and 81 overlap within the microfluidic filtering device 68 at overlap region 92. At overlap region 93, fluid passes from the microfluidic filtering device into the control microfluidic coupling devices 20b. At overlap region 94, fluid passes from the microfluidic filtering device 68 into the capture microfluidic coupling devices 30.

[0055] In operation, a sample plug is injected at the inlet port 70 using a syringe pump at a constant flow rate of 5 microliters per minute. The fluidic sample then passes into channel 74 where it is distributed among the three outlet ports 75. The fluid enters the microfluidic couplers 20a and is transported to the inlet ports 85 of the second device 68. The fluid passes across filter regions 86, bypasses the overlap region 92 and is transported to the exit region 93 into the control microfluidic couplers 20b. In the embodiment shown, the filter region 86 does not contain any filter material, although numerous types of filter materials could be added to the filter regions 86 by conventional means. Once sufficient fluid has passed into the control microfluidic couplers 20b, sufficient pressure may be applied to the outlets 26 to increase the pressure within the device 68 and overcome the impedance 92. The fluid then passes into the elution channel 81 and passes into the capture microfluidic coupling device 30. Once sufficient fluid has entered the capture microfluidic couplers 30 the devices can be removed from the microfluidic filtering device 68 for further analysis. An output port 26 of one of the coupling devices 20b, 30 can be blocked by folding such a device back on itself to cover the outlet port 26.

[0056] Microfluidic coupling devices according to the present invention can be used to supply fluids to an external microfluidic device and receive fluids from an external microfluidic device. Referring to **FIG. 4A**, a microfluidic coupling and distribution system 95 includes a microfluidic distribution device 67a constructed in the same manner as the device 67 shown in **FIGS. 3A-3B**. Also provided are microfluidic coupling devices 20c and 20d, which are substantially similar to the couplers 20b of **FIGS. 3A-3B**. A pipette tip coupling block 100 having a tapered fluid receptor 101 is connected to the coupler 20c and is shaped to fit a standard pipette tip 102 snugly. The assembled system 95 is shown in **FIG. 4B**. In use, the microfluidic coupler 20c is oriented with the ports facing upward, and the inlet port is connected to the outlet port 104 of the pipette tip coupling block 100. The outlet port of the microfluidic coupler 20c is connected to the inlet port 70 of the microfluidic distribution device 67a. A pipette tip 102 filled with liquid is inserted into the pipette tip coupling block 100. Fluid is injected from the pipette through the coupling block 100, through the coupling device 20c, into the distribution device 67a, and finally through the outlets ports 73 into the output microfluidic coupling devices 20d. Thereafter, the microfluidic coupling device 20c may be removed from the pipette tip coupling block 100 and another separate microfluidic device (not shown) can be connected to the coupling block 100 in a similar manner.

[0057] In alternative embodiments, coupling blocks can be constructed to permit introduction using various methods or structures, *e.g.*, capillary tubes. In certain embodiments, a negative pressure can be applied at one or more the outlet ports of a

microfluidic device to draw the fluid through a microfluidic coupler and into the device. If desired, small aliquots of fluid can be inputted in this manner.

[0058] In a further embodiment, a microfluidic multi-chip module (MCM) system contains electrodes to perform various types of detection and or electroactive manipulation. Referring to **FIG. 5A**, a microfluidic MCM platform 146 is constructed that is capable of joining three distinct microfluidic modules 120-122. The platform 146, which includes an electrode-bearing base member 140 and two stencil layers 131, 130, serves as a microfluidic coupling device for the three microfluidic modules 120-122. The distinct microfluidic modules 120-122 could be constructed from any number of different manufacturing techniques including silicon fabrication techniques, silicone replications, hot embossing, molding, injection molding, etc. These modules 120-122 can perform a variety of fluidic functions. A first microfluidic module 120 has an inlet port 123 on the bottom side and an exit port 124 on the top side. A second microfluidic module 121 has both inlet port 125 and exit port 126 on the bottom side. A third microfluidic module 122 has an inlet port 127 on the top side and an exit port 128 on the bottom side.

[0059] Referring to **FIGS. 5A-5B**, the base member 140 of the MCM platform 146 contains electrodes that may be constructed using circuit board technology. The top surface 142 of the circuit board substrate 140 forms the bottom layer of microfluidic channels 133, 134 in the assembled system 115 (as shown in **FIG. 5C**). Electrodes 141 are placed along the endpoints and center of each channel 133, 134. The electrodes 141 are made by forming holes in the circuit board laminate 140 in positions where the electrodes 141 are to be located, followed by soaking the substrate 140 in a copper solution to cover the inside surfaces of the holes, then patterning and etching the bottom surface and top surface to form copper lines on the bottom side 144 and electrodes 141, 143 on both sides. Finally, a conductive epoxy may be then screened into the holes that are to form the electrodes 141. Gold is preferably plated onto the electrodes 141 to form a well-defined electrode surface and the edges of the electrodes 141 may be covered with a layer of solder mask, if so desired. In this manner, the upper surface of the top layer 142 can actually be solder mask rather than the circuit board substrate itself.

[0060] In addition to the circuit board base member 140, the MCM platform further includes stencil layers 130, 131. The stencil layer 131, which defines two channels 133, 134, may be constructed from single sided tape such as 2 mil (50 micron) polyester carrier with an acrylic adhesive. The stencil layer 130, which defined various inlet/outlet ports 132, may be constructed from double sided adhesive, such as 0.5 mil (13 micron) polyester carrier with acrylic adhesive on both sides. The microfluidic MCM system is assembled by

adhering the two stencil layers onto the circuit board layer 140. The microfluidic modules 120-122 can then be adhered to the MCM platform 146 for use.

[0061] The assembled system 115 is shown in **FIG. 5C**. In this example, fluid is injected into the inlet port 127 of device 122. The third module 122 acts on the fluid to perform its function. The fluid then leaves the outlet port 128 and enters the channel 134 of the MCM platform 146. The fluid passes through channel 134 and enters the second module 121 at inlet port 126. Again, the second module 121 performs its function and the fluid exits at port 125. The fluid enters the second channel 133 of the MCM platform 146 and passes into the inlet port 123 of the first module 120. The first module 120 acts on the fluid and thereafter the fluid exits at exit port 124. The electrodes 141 within the MCM channels may be used for a number of functions, such as inducing electrokinetic flow or electrophoresis, or providing electronic detection such as electrochemical detection or impedance measurements. The electrodes 141 of the MCM platform 146 can be connected to the outside world through an edge card connector, since the electrodes lead to plated pads 145 located on the back side of the circuit board substrate 140. These pads 145 are spaced with standard edge card spacing for convenient use.

[0062] The MCM system 115 is preferably used for continuous processing. Alternatively, once the microfluidic modules 120-122 have performed their function, one or all of the modules can be removed from the MCM. The modules 120-122 can be reused in other configurations or discarded. The MCM platform 146 can be reused with new modules or discarded.

[0063] In an alternative embodiment, if no electrode manipulation or testing is required, then the circuit board substrate 140 in **FIGS. 5A-5C** can be replaced with a solid layer. In a further alternative embodiment, a flex-tape circuit board 140 can be provided to render the entire MCM platform 146 flexible.

[0064] The present invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed, since these embodiments are intended merely to illustrate certain aspects of the invention. All equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

[0065] The disclosures of all references cited herein are incorporated by reference in their entireties.

What is claimed is:

1. A modular microfluidic system [35, 65, 95, 115] comprising:

a plurality of discrete microfluidic modules [36, 67, 68, 67a, 102, 146] each module being adapted for rapid attachment to or detachment from one or more other modules and being capable of performing a desired function independently of any other module; and

at least one microfluidic coupling device [20, 30, 20a, 20b, 20c, 20d, 146] for communicating fluid between the plurality of microfluidic modules, the at least one coupling device being fabricated from multiple layers [21, 22, 23, 27, 140, 131, 130] and including a fluidic inlet port [25, 26, 132], a fluidic outlet port [25, 26, 132] and at least one sandwiched stencil layer [22, 131] having a microfluidic channel [24, 133, 134] formed therein, the channel being in fluid communication with the fluidic ports.

2. The modular microfluidic system of claim 1 wherein the at least one microfluidic coupling device provides a removable fluidic connection between the plurality of microfluidic modules.

3. The modular microfluidic system of claim 1 wherein the at least one microfluidic coupling device includes at least one outer surface having an adhesive for mating with at least one microfluidic module.

4. The modular microfluidic system of claim 3 wherein the adhesive is non-permanent to permit the at least one microfluidic coupling device to be removed intact from a microfluidic module.

5. The modular microfluidic system of claim 3 wherein the adhesive outer surface or the at least one stencil layer is an adhesive tape selected from the group consisting of: pressure-curing tapes, heat-curing tapes, light-curing tapes, and chemically-curing tapes.

6. The modular microfluidic system of claim 1 wherein the at least one microfluidic coupling device is composed of materials selected from the group consisting of: papers, foils, and plastics.

7. The modular microfluidic system of claim 1 wherein the at least one microfluidic coupling device is flexible or malleable to permit the coupler to communicate fluid while disposed in a non-planar orientation.

8. The modular microfluidic system of claim 1 wherein the at least one microfluidic coupling device includes a plurality of discrete, integral electrodes [141].

9. The modular microfluidic system of claim 8 wherein the plurality of discrete electrodes are used for at least one of the following functions: providing electronic detection, promoting electrokinetic flow, and providing thermal control.

10. The modular microfluidic system of claim 1 wherein at least one microfluidic coupling device has an associated semi-permeable membrane [27] that permits the passage of gases but not the passage of liquid.

11. The modular microfluidic system of claim 1 wherein at least one microfluidic module includes a fluidic coupling block [102].

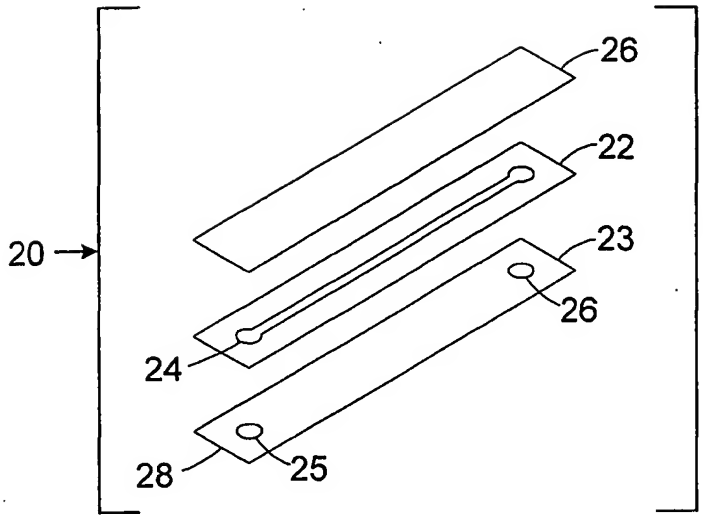

FIG._1A

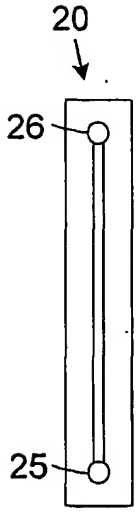

FIG._1B

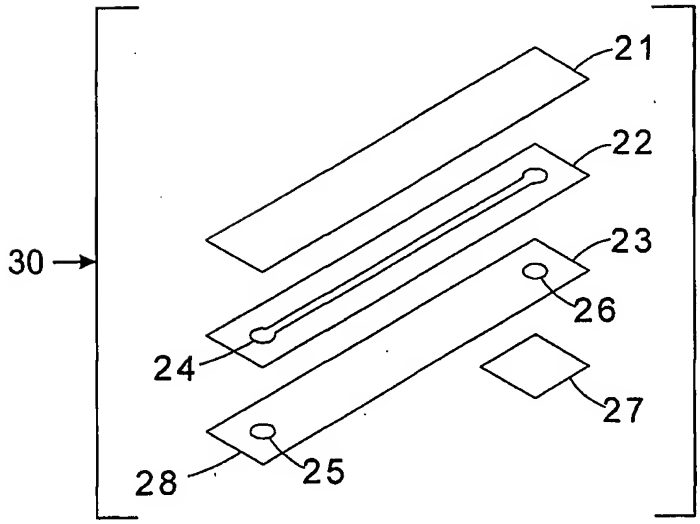

FIG._1C

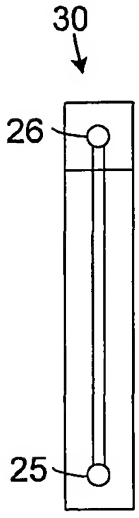

FIG._1D

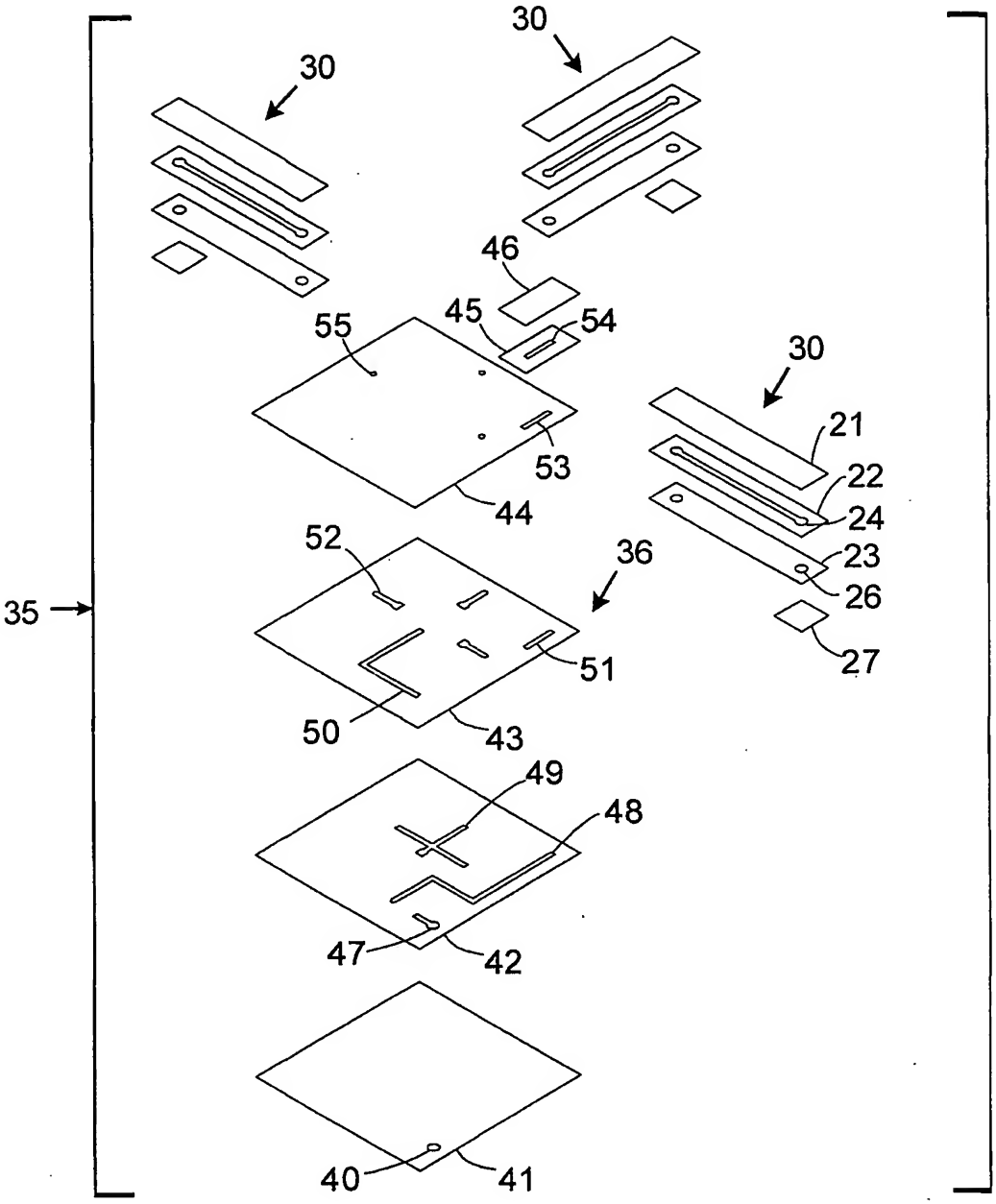
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FIG._2A

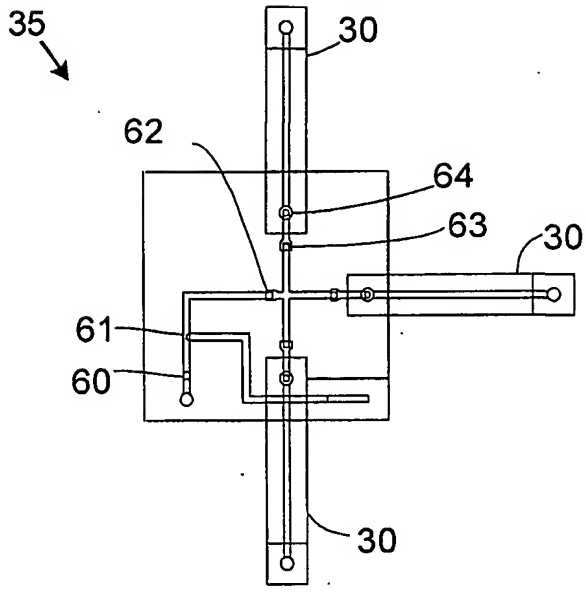

FIG._2B

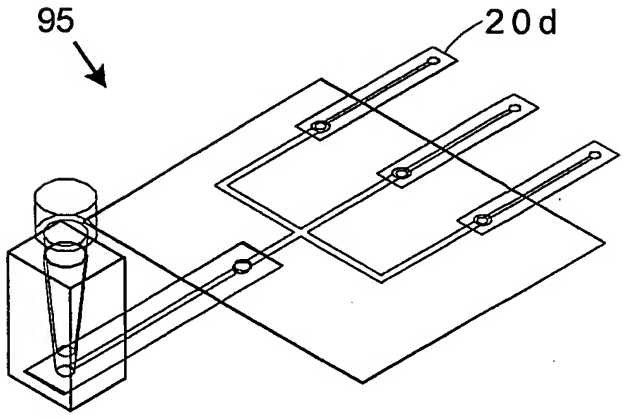

FIG._4B